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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/441,654	11/12/1999	SHAM-YUEN CHAN	MSB-7263	4743

20306 7590 10/23/2002

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EXAMINER
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BUGAISKY, GABRIELE E

ART UNIT	PAPER NUMBER
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1653

DATE MAILED: 10/23/2002

17

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

Application No.

09/441,654

Applicant(s)

CHAN, SHAM-YUEN

Examiner

Gabriele E. BUGAISKY

Art Unit

1653

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 13 May 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 2,6-9,15,18-21,25 and 26 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 2,6-9,15,18-21,25 and 26 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on \_\_\_\_\_ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

## Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) \_\_\_\_\_.
- 4) ☐ Interview Summary (PTO-413) Paper No(s) \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

### **DETAILED ACTION**

The amendment of 5/22/2002 is acknowledged. Claims 3-5 and 16-17 have been cancelled and new claims 25-26 have been submitted. Claims currently pending and under consideration are 2, 6-9, 15, 19-21 and 25-26.

#### ***Specification***

The disclosure remains objected to because of the following informalities: patent application numbers remain in the disclosure.

Appropriate correction is required.

#### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 2 and 6-9 remain rejected and claim 2 is newly rejected under 35 U.S.C. 102(b) as being anticipated by Kawaguchi *et al.* Kawaguchi *et al.* provides for purification of human hepatocyte growth factor activator inhibitor type 2 from conditioned medium of MKN45 cells. The reference is deemed anticipatory for the claimed subject matter because the primary amino acid sequence of human hepatocyte growth factor activator inhibitor type 2 is identical to instant SEQ ID NO:1 and because the protein is purified from human cells, it inherently is glycosylated; indeed, for SDS-PAGE analysis, the protein is deglycosylated (see last paragraph, column 1,

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page 27550) . With respect to the recited pharmaceutically acceptable carrier, the protein activity was assayed in PBS.

Applicant's arguments filed 5/2002 have been fully considered but they are not persuasive. It is stated that the reference is not anticipatory because it is silent on sialic acid content. The glycosylation pattern and sialic acid content is an inherent feature of mammalian bikunin; indeed, the literature recognizes that bikunin contains sialic acid (see, e.g., YUKI *et al.*) and that it contains N-acetylneuraminic acid (see, e.g., HOCHSTRASSER *et al.*, page 1360, first paragraph).

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 15 remain rejected and claim 18-21 and 26 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Gentz *et al.* in view of Gribben *et al.* and Hotchkiss *et al.* Due to a bookkeeping error, the previous Action stated that claims 9-15 were rejected; the rejection of claim 9 is withdrawn..

The Gentz reference provides for production of TFPI-3, a two domain glycosylated Kunitz protein inhibitor Its sequence is identical to SEQ ID NO:1. In example 5, the first Kunitz

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domain is assayed. That domain was produced by *E. coli* and not by mammalian cells. Gribben *et al.* show that antibodies develop to recombinant human GMS-F that is not O-glycosylated and Hotchkiss *et al.* show that the carbohydrate structure of recombinant tissue factor plasminogen activator has an effect on the rate of clearance. Neither examines glycosylated TFPI-3. Gribben *et al.* suggests that antigenicity of human proteins may be relevant to the choice of host system in production of proteins for clinical use. In order to provide the domain 1 of Gentz *et al.* in a form that neither elicits antibodies & has a relatively long half life, it would have been obvious to one of ordinary skill in the art at the time of the invention to express domain I in mammalian cells, with a reasonable expectation of success.

Applicant's arguments filed 5/2002 have been fully considered but they are not persuasive. IT is stated that none of these references teaches or remotely suggests sialic acid modification of proteins. It is stated that there is absolutely no motivation to combine references, as the Gribben and Hotchkiss references are to entirely different proteins, This is not persuasive.. The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference or that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art (*In re Keller*, 208 USPQ 871, 881). First, as discussed above, human bikunin is known to be a glycoproteins that has sialic acid residues when produced in mammalian cells. Both Gribben and Hotchkiss deal with recombinant blood proteins and the effects of glycosylation on the proteins. Since the intended use of blood proteins is clinical in nature, results obtained with other such recombinant proteins is indeed relevant. Both the Gribben and Hotchkiss references show that

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for two different blood proteins, the glycosylation pattern IS important, and for two different reasons-antigenicity and clearance. One of skill in the art would thus expect that to minimize such problems with any recombinantly produced blood protein, one would want to use mammalian cells as the host system to produce a normal glycosylation pattern. Since TFPI3 is a blood protein, again, one would have ample reasons to heed the teachings of the Gribben and Hotchkiss references and expect that for clinical applications, the first Kunitz domain of the TFPI3 of Gentz *et al.* should be produced in mammalian cells to demonstrate a mammalian glycosylation pattern.

#### ***Conclusion***

No claims are allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Fritz *et al.* describe bikunin variants and state in column 4, lines 27-29 that "If the aim is to achieve glycosylation similar to that present in mammal, systems which glycosylate correctly must be chosen."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gabriele E. BUGAISKY whose telephone number is (703)308-4201. The examiner can normally be reached on 8:15-12:15 M, 8:15-1:15 Tu-F.

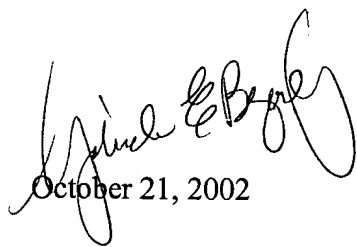
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher SF Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are 703 308-4242 for regular communications and 703 308-4242 for After Final communications.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 708 308-0196.



October 21, 2002

Gabriele E. BUGAISKY  
Primary Examiner  
Art Unit 1653

**GABRIELLE BUGAISKY  
PRIMARY EXAMINER**